Dear Grant Team, Please find attached the following in one pdf

1. Letter of Intent from the applicant.
2. Proposed researched summary
3. Appendix-Figure 1
4. Impact Statement
5. Public Non-Scientific summary
6. Budget Invoice
7. Budget Details
8. Names of Investigators (PI and Co-PI)
9. Statement of support from the applicant's institution.

Thank You.

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Verspeeten Family Cancer Centre
London Health Sciences Centre

Dear Geoffrey Ogram Memorial Research Grant team,

The Verspeeten Family Cancer Centre (VFCC) at London Health Sciences Centre (LHSC) is seeking support for an innovative project aimed at improving early diagnosis and detection of molecular alterations in advanced non-small cell lung cancer (NSCLC) patients, enabling earlier treatment and advancing precision oncology through circulating tumor DNA (ctDNA) testing. We are applying for the Geoffrey Ogram Memorial Research Grant (GOMRG) and are requesting CAD 25,000 to fund this initiative.

The current project will address the critical gap in the early detection and treatment of advanced NSCLC patients. Although effective, traditional tissue-based biopsy methods are time-consuming and invasive and often delay diagnosis and treatment initiation. A second or repeat tissue biopsy to get enough tissue samples, in some cases, further delay the process and cause increase patient distress. In cases of advanced NSCLC, especially in enriched populations with a higher likelihood of targetable mutations such as young individuals, non-smokers or former light smokers and those with Asian ancestry, these delays can significantly impact patient outcomes. ctDNA testing offers a non-invasive, early and reliable alternative for detecting molecular alterations, potentially accelerating treatment initiation and improving patient outcomes.

This project will respond to this issue by comparing the turnaround time for molecular results between ctDNA and tissue biopsy samples, assessing concordance rates, and exploring the feasibility of ctDNA as an early detection tool in routine clinical practice. The focus on enriched populations aims to maximize the likelihood of detecting actionable mutations, which can lead to more precise and personalized treatment initiation as soon as possible and maximizing cost effectiveness. By reducing the time between early molecular detection and treatment initiation, this project can potentially enhance the quality of care for patients with advanced NSCLC, improving survival rates and quality of life and providing valuable data to support the broader integration of ctDNA testing into clinical practice.

The project will evaluate ctDNA testing using the Guardant360 assay as an early detection tool in patients with advanced NSCLC, and it will recruit 20 patients with a higher pretest probability of their cancers harboring a genomic alteration. The VFCC, with its fully staffed and supported biorepository, will process and store plasma samples for biomarker research. These resources enable the collection, processing, and analysis of ctDNA with minimal logistical challenges, ensuring the study's feasibility. The study will compare the turnaround time for molecular results from ctDNA testing versus usual tissue biopsy, aiming to demonstrate the time-saving potential of ctDNA for earlier treatment initiation. The project will also assess the concordance between

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ctDNA and tissue-based molecular testing for actionable mutations, such as EGFR, ALK, ROS1, etc. Other key activities include collecting patient demographic data, conducting blood draws, processing plasma samples, and analyzing molecular results.

The Guardant360 liquid biopsy test, which uses a simple blood sample, offers treating physicians comprehensive genomic results aligned with clinical guidelines within seven days of receiving the sample. This advanced test supports personalized treatment decisions for patients with advanced-stage solid tumors by identifying potential therapeutic options and relevant clinical trials. This study's estimated total cost for 20 tests is approximately CAD $23,000 with an additional $1,600 and $400 CAD for the research coordinator and phlebotomy costs, respectively.

We would be happy to provide any additional information or details the foundation may require regarding this project. We sincerely appreciate your time and consideration of our submission for the Geoffrey Ogram Memorial Research Grant. We welcome the opportunity to discuss the project further and answer any questions you may have. We are enthusiastic about this study's potential to advance precision oncology and kindly request your support in providing the necessary funding to make this vital research possible. Thank you once again for your attention and consideration.

Sincerely,

Daniel Breadner, MD FRCPC
Medical Oncologist, Verspeeten Family Cancer Centre
Assistant Professor and Clinician Researcher, Western University
A3-913, 800 Commissioners Road East
London, Ontario, Canada, N6A5W9
Fax: 519 685 8624

Title

CtDNA testing at/during the **D**iagnostic **A**ssessment **P**rocess for **E**arly **D**etection in Patients with NSCLC. (ctDNA DAP-ED).

Background and Rationale

Lung cancer is foremost the leading cause of cancer deaths in Canada, with over 20,700 projected deaths in 2024 (1). Non-small cell lung cancer (NSCLC) type accounts for more than 80% of the cases (2). Circulating tumor DNA (ctDNA) via liquid biopsy is a minimally invasive method to detect cancer, and it has gained significant attention, with blood samples being the most commonly utilized method. These samples include ctDNA, which originates from tumour cells and contains mutations, offering valuable insights into tumor dynamics and molecular changes in NSCLC (3).

The inspection of ctDNA has become a crucial tool in managing NSCLC, helping with diagnosis, treatment decisions, and disease monitoring. It detects minimal/molecular residual disease (MRD) and resistance mutations, such as EGFR T790M, which confers resistance to early-generation EGFR inhibitors. Testing NSCLC patients for mutations via next-generation sequencing (NGS) testing, such as EGFR, ALK, ROS1, NTRK, KRAS G12C, RET, BRAF, MET exon 14 skipping, ERBB2, and HER2 overexpression is now becoming a standard of care (4). CtDNA can be used for upfront testing of these molecular alterations to identify mutations that can be treated with targeted therapy (5).

Many lung cancer patients require multiple biopsies for diagnosis and tissue-based biomarker testing. ctDNA testing has shown high concordance and reliability compared to traditional tissue tests, potentially reducing the need for repeated biopsies and offering faster results on the presence or absence of NSCLC oncogenes (5). In a previous quality improvement study at the Verspeeten Family Cancer Centre (VFCC) at London Health Sciences Centre, the Lung Diagnostic Assessment Program (DAP) considered ctDNA testing for patients likely to have advanced NSCLC based on imaging suggestive of stage IV disease. This approach addressed the long turnaround time (4–6 weeks) and failure rates of molecular testing post-biopsy, and shortened time to see a medical oncologist and the time to start treatment (submitted for publication).

This prospective study seeks to estimate the effectiveness of ctDNA analysis using the Guardant360 (G360) assay for early detection of molecular alterations in a highly specified group of patients with a high plausibility of advanced NSCLC. Given the enriched potential for actionable mutations in the selected population, ctDNA testing could provide a more timely and accurate assessment of tumor genomics, reducing the reliance on traditional tissue biopsies. The rationale for this study is based on the need for improved diagnostic tools to identify actionable mutations early, facilitating targeted therapy decisions and enhancing clinical outcomes in patients with advanced NSCLC (figure 1).

Objectives:

Primary Objective:

1. To compare the turnaround time for molecular results between ctDNA and tissue biopsy samples, from the time of DAP consultation.
2. To access the concordance rates between ctDNA and tissue-based molecular testing for actionable mutations.
3. To assess the prevalence of actionable alterations in an enriched population.

Secondary Objective:

1. To determine the time from the medical oncology consultation to the initiation of first-line treatment.

2. To assess the feasibility of ctDNA testing as an early detection tool in routine clinical practice for enriched patients with advanced NSCLC.

Exploratory Objective:

3. To evaluate the cost effectiveness analysis (CEA) of ctDNA testing.

Endpoints

Primary endpoints:

1. To evaluate the difference in median time (in days) between the availability of ctDNA molecular results and tissue biopsy molecular results, from the time of DAP consultation.
2. The proportion of actionable mutations such as EGFR, RAS, ALK, etc., detected by ctDNA testing that are concordant with tissue-based molecular testing.
3. To determine the number of patients who tests positive for specific actionable mutation in the enriched population.

Secondary endpoints:

1. To determine the median time (in days) from the medical oncology consultation to the initiation of first-line treatment.
2. The feasibility of ctDNA in clinical practice will be measured by the proportion of tests completed within the defined timeframe, successful blood draws and sample processing rates, and clinician feedback on the ease of integrating ctDNA results into practice.

Exploratory endpoints:

3. Cost effectiveness analysis will be considered upon collaboration with experts.

Study Design

Study type: This will be a prospective cohort study. It will follow a group of patients with a high likelihood of advanced NSCLC undergoing ctDNA testing as part of VFCC Lung-DAP.

Study population

Inclusion Criteria:

1) Enriched pretest likelihood of an actionable alteration a) Patients age 50 or less (b) Non-smoker or light former smoker (reformed for a greater number of years than pack years of tobacco use) or (c) Asian born or ancestry
2) Clinical stage IV disease
3) ECOG performance status 0-II.

Exclusion Criteria: a) Patients age > 50 b) Patients with contraindications to blood draw or who declined to participate c) Patients with a history of other malignancy in the last five years (except non-melanoma skin cancer and low-risk controlled prostate cancer).

Study Procedures

Data Collection: Study participants will provide demographic information, including age, biological sex, current medications, and medical history. We will collect additional information later, including cancer type, document stage, molecular sequencing results, date of medical oncology consultation, treatments recommended, and date of treatment initiation. Additional data may be retrieved from the patient's electronic medical record (EMR). All information will be securely stored in REDCap, a database managed by Lawson Health Research Institute, ensuring confidentiality through unique study ID numbers linked to personal data. Only authorized study team members will access the Master List, and any shared data with collaborators will be de-identified and limited to necessary information for analysis.

Sample size: We plan to include approximately 20 patients in our study.

Data analysis: All continuous variables will be recorded as means and medians with standard deviation and interquartile ranges as appropriate, and all categorical variables will be reported as frequency counts and proportions.

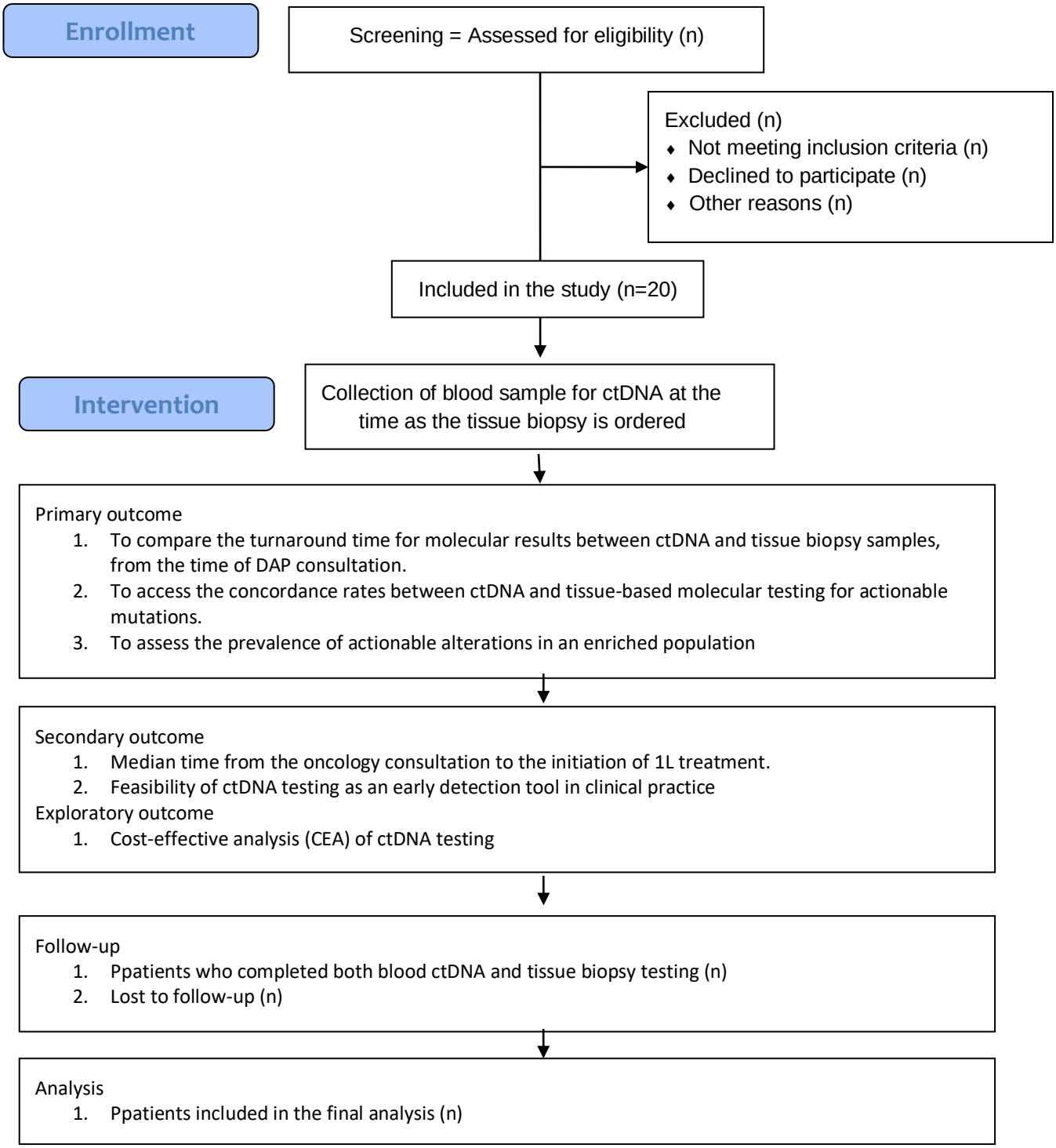
Significance

1. ctDNA testing is a valuable non-invasive tool for managing lung cancer, providing real-time monitoring and early detection of genetic mutations.
2. This approach allows clinicians to personalize treatment plans and identify actionable mutations, facilitating targeted therapies while reducing unnecessary procedures.
3. Integrating ctDNA testing into standard care can significantly enhance patient outcomes and improve quality of life.

References:

1. Canadian Cancer Society Cancer Statistics 2024 [cited 2024 Sep 24, 2024]. Available from: https://cancer.ca/en/research/cancer-statistics/canadian-cancer-statistics.
2. Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. Mayo Clin Proc. 2008;83(5):584-94.
3. Khan SR, Scheffler M, Soomar SM, Rashid YA, Moosajee M, Ahmad A, et al. Role of circulating-tumor DNA in the early-stage non-small cell lung carcinoma as a predictive biomarker. Pathol Res Pract. 2023;245:154455.
4. Wang HY, Ho CC, Lin YT, Liao WY, Chen CY, Shih JY, et al. Comprehensive Genomic Analysis of Patients With Non-Small-Cell Lung Cancer Using Blood-Based Circulating Tumor DNA Assay: Findings From the BFAST Database of a Single Center in Taiwan. JCO Precis Oncol. 2024;8:e2300314.
5. Leighl NB, Page RD, Raymond VM, Daniel DB, Divers SG, Reckamp KL, et al. Clinical Utility of Comprehensive Cell-free DNA Analysis to Identify Genomic Biomarkers in Patients with Newly Diagnosed Metastatic Non-small Cell Lung Cancer. Clin Cancer Res. 2019;25(15):4691-700.

Figure 1: CtDNA DAP-ED



Impact Statement

Jurisdictions across Canada are starting to fund liquid biopsies for ctDNA in selected patients with NSCLC. This is typically restricted to individuals who have a tissue diagnosis but inadequate tissue for molecular testing. This study seeks to demonstrate that a larger group of Canadians can benefit from this testing which will allow them to get an earlier diagnosis and full molecular testing, and allow many patients to start treatment sooner. This study will be published and will include a cost effectiveness analysis, allowing it to be considered in health technology assessments by Provincial cancer authorities. This study will positively impact the lives of the participants, build evidence for the use of ctDNA testing at the time of first lung cancer assessment, and influence future policy decisions as funded indications for plasma-based genomic profiling expands.

CtDNA Lung-DAP ED Public (Non-scientific) Summary

Lung cancer remains the number one cause of cancer death in Canada for both men and women. When it is diagnosed as stage IV disease, it means the cancer has already spread to either the opposite lung or outside the lung somewhere else in the body, like in the liver, bones, brain, etc. The treatment for stage IV lung cancer is most often non-curable, and the primary goal of treatment is to control the disease symptoms, improve the quality of life and prolong life. To do so, starting treatment as early as possible is vital to slow down the further spread or new symptoms. There are many treatment options for stage IV lung cancers, depending upon the presence or absence of markers or mutations called "molecular targets."

An invasive procedure to obtain a tissue sample for biopsy is usually recommended to confirm the diagnosis. This is performed by inserting a needle or a small tool into the body to reach the tumor, often through the chest or sometimes by going down through the mouth or throat. It involves making a small cut or using a thin needle. Then, the sample is examined under the microscope to see if the cancer cells are present or not. An adequate tissue sample is required to report the findings. Many patients have to undergo a second tissue biopsy in case of inadequate tissue samples. This is followed by further tests of markers on the tissue sample, which generally takes 2 to 6 weeks. Early cancer detection and subsequent identification of these abnormal molecular markers are important to help start treatment as soon as possible.

Fortunately, new tests are being developed and are available to detect cancer cells as well as the abnormal markers associated with them. These tests are non-invasive; the most commonly utilized method is the blood sample. These tests are called "liquid biopsies," and they measure small pieces of circulating DNA, small proteins or other signals, including different markers such as EGFR, KRAS, ALK, etc. Compared to tissue biopsy, these liquid biopsies provide results as early as two weeks. One example of a cancer liquid biopsy test is the Guardant360 (G360) circulating tumor DNA assay, which can detect abnormal molecular markers with very high sensitivity.

In our study, certain patients with clinical stage IV lung cancers who are selected for a tissue biopsy procedure will be asked to participate. Participants would provide a blood sample when the biopsy is ordered. The blood sample will be used to perform the circulating tumor DNA testing using a G360 assay to identify cancer cells and any abnormal molecular markers. Participants and their clinicians will receive the G360 report, even if the tissue testing results are not yet available. This study is based on the need for improved diagnostic tools to identify specific cancer markers early, facilitating treatment decisions in stage IV lung cancers and enhancing the effectiveness of medical care for these patients.

Invoice - ctDNA Transformation Pilot

From: **Guardant Health, Inc.**
3100 Hanover St
Palo Alto, CA 94304
United States

To: **London Health Science Centre**
800 Commissioners Road E
London, Ontario, N6A 4L6
Canada

Invoice #: LHSC-Transformation-01

Product	Description	
Guardant360® (74 Genes)	Based on a simple blood sample, the Guardant360® liquid biopsy test provides treating physicians with guideline-recommended comprehensive genomic results within 7 days of sample receipt. Guardant360® enables informed treatment decisions in patients with advanced-stage solid tumors. Possible treatment options and clinical studies are identified and presented in a corresponding report.	
	Quantity	**Rate***
	List Price	$3,490 USD / Sample
	Exceptional Transformation Pilot Price	$1,000 USD / Sample
	3x	Free Transformation Tests
	17x	Paid Transformation Tests
	Total	**$23,000 CAD**

The *Transformation Pilot pricing is confidential* and cannot be shared with others. The Transformation Pilot is limited to a total of 20x tests and/or ends 31st of December 2024.

Samples for the *Guardant360® Transformation Projects are to be paid upfront. The payment terms are net 30 days. Guardant Health Inc standard terms and conditions apply.

If you have any questions do not hesitate to contact us.

Client Services International
Email: international@guardanthealth.com

Account Name: Guardant Health, Inc. // **Bank Name:** Chase // **Transit (for Wires):** 021000021 // **SWIFT Code:** CHASUS33 // **Bank ABA:** 322271627 // **Account #:** 100084695
Reference: PM-Transformation-1

Item	unit cost	Qty	
Guardant ctDNA assay -$1000 USD	$1,353.00	17	$23,001.00
Additional Guardant Assays	Free	3	$0.00
Research Coordinator			$1,600.00
Vials (Streck, EDTA, CryoVials, centrifuge)	Provided		$0.00
Phlebotomy cost	$20/draw	20	$400.00
Shipping	Provided		$0.00
Plasma Processing and Storage*			
Knowledge Dissemination*			
Total			$25,001.00

Plasma processing and storage - supported by the Department of Oncology
Knowledge Dissemination - Article
processing fees covered by department for
certain journals. Fellowship stipend will
cover conference fees and travel

Project Title

CtDNA testing at/during the **D**iagnostic **A**ssessment **P**rocess for **E**arly **D**etection in Patients with NSCLC. (ctDNA DAP-ED).

Principal Investigator:
Dr. Daniel Adam BREADNER, MD

Co-Principal Investigator:
Dr. Saqib Raza KHAN, MD.

Schulich MEDICINE & DENTISTRY

Department of Oncology

September 23, 2024

RE: Letter of Institutional Commitment

To the Geoffrey Ogram Memorial Research Grant Selection Committee,

I am pleased to write this letter to express my strong support for this grant proposal for the Lung Cancer Canada Geoffrey Ogram Memorial Research Award, titled “Circulating Tumor DNA in the Lung Diagnostic Assessment Program (ctDNA-DAP-EarlyDetection)”.

The Verspeeten Family Cancer Centre (VFCC) at London Health Sciences Centre has a Lung-Diagnostic Assessment Program (Lung-DAP) that is involved in the investigation of over 1000 patients per year; over 300 of whom are found to have at least locally advanced non-small cell lung cancer annually. The VFCC has a fully staffed and supported BioRepository to support biomarker research, including plasma processing and storage. This study requires only 20 selected patients with advanced lung cancer, so their target is highly feasible.

Dr. Breadner has a track record of success in projects working with the Lung-DAP and in ctDNA biomarker studies. We support him in this endeavor and appreciate your consideration to support this important work.

Please do not hesitate to contact me if you have any queries.

Regards,

Michael C. Ott, MD, MSc, MHPE, FRCSC, FACS, FASCRS
General and Colorectal Surgery
Professor, Schulich School of Medicine & Dentistry
Department of Surgery & Surgical Oncology
Chair Department of Oncology
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